

Criteria for Discontinuation of HIV-1 p24 Antigen Screening of Source Plasma: Current Thinking

BACKGROUND

When HIV-1 p24 antigen testing was instituted in March, 1996, for the screening of blood and plasma donors, it was recognized that antigen tests were less sensitive than nucleic acid tests (NAT), particularly NAT for viral RNA. Based on seroconversion data, it was estimated that NAT could eventually reduce the window period for HIV by an additional 5 days (from 16 days to 11 days) over the reduction achieved by antigen testing when compared with detection of antibodies determined using the most sensitive antibody tests (i.e. from 22 days to 16 days). However, NAT was only feasible at the time in a research setting, and it was decided to adopt p24 antigen testing as an interim measure for interdicting window period donations.

Since the initiation of antigen testing over four years ago, according to data from the American Red Cross, a total of 10 window period units have been detected by HIV antigen testing alone in the U.S. and Puerto Rico. In HIV infection p24 antigen and viral RNA are direct viral markers which display similar patterns in the early window phase of infection. With the implementation under IND of NAT testing of U.S. donors of Whole Blood and Source Plasma using pooled donor plasma which has been sparked by European requirements, the feasibility of replacing HIV-1 p24 antigen testing with NAT testing for early detection of window period donations has been raised by many in the field..

FDA's current thinking

At the BPAC meeting held on March 25, 1999, FDA announced its thinking on the issue of criteria for replacement of p24 with NAT. These and a few additional points that were added subsequent to the BPAC meeting are outlined below. An applicant would be required to submit the following data to justify replacing p24 antigen testing with NAT minipool testing or with NAT testing of individual plasma donations:

1. Data showing that the sensitivity of the NAT test is equal to or greater than that of p24 antigen testing in the window period.
 - a) NAT testing must be able to detect all available repository p24-positive antibody-negative window period blood donation specimens detected since the start of p24 screening when those specimens are included in a plasma pool. (whether or not they remain p24-positive when diluted in the pool) or

when tested individually.

- b) Data showing that NAT testing can detect p24-positive samples in commercial plasma donor seroconversion panels when tested individually or with adequate sensitivity to address the dilution factor due to pooling (i.e., when those samples are diluted in a plasma pool).
 - c) Data from clinical trials comparing the relative frequencies of detection for antigen testing and NAT testing in prospective studies of Whole Blood and plasma populations. The number of p24-positive or NAT-positive window period units required would be established prior to such clinical trials by statistical evaluation and agreed to by FDA. This prospective data will include analysis of the NAT-positive rate for p24-positive antibody-positive as well as p24-positive antibody-negative specimens.
2. Data showing that NAT testing is able to detect all HIV variants (including HIV-1 group M subtypes A through G and group O) that would be detected by the licensed p24 antigen tests. This can be provided by testing well-characterized p24-positive antibody-positive samples from HIV-1 variants (10 of each HIV-1 group M subtype A-G). A combination of naturally-occurring human serum samples and cell culture fluids from HIV-1 variants spiked into normal plasma should be used to demonstrate the sensitivities of the p24 assay and the NAT test. FDA may work with industry to identify and collect such specimens and establish a validation panel.
 3. Data from reproducibility studies of the NAT testing method in routine operational settings to demonstrate that even weakly reactive p24 antigen samples will be detected by the NAT test on multiple days, instrument systems, operators, and product lots.
 4. The NAT testing method must be licensed by FDA. (NAT testing under IND will not be allowed to replace p24 antigen testing).
 5. A testing organization must submit an IND or amend an existing IND that outlines specific clinical trials to substantiate a claim of replacing HIV p24 antigen testing with NAT testing. Because of differences in NAT methods and INDs, licensure of NAT testing with a substantiated claim for replacement of p24 antigen testing for a specific testing organization will form the basis for discontinuation of p24 antigen testing by that organization using the licensed NAT method. This approach will be adopted rather than an industry-wide withdrawal of p24 antigen testing recommendations by FDA.